REMARKS

In view of the foregoing amendments and the following representations, reconsideration and allowance of the above-identified application is respectfully requested.

Claims 2, 23 and 27 have been canceled without prejudice. Applicants may pursue the subject matter of these claims in a subsequent application. Claims 1, 3-22, 24-26 and 28-29 are in the present application.

In the Office Action on page 2, paragraph 3, the Examiner rejected claim 27 under 35 U.S.C. § 112 second paragraph for being indefinite. Although Applicants respectfully disagree with the Examiner's rejection, Applicants have cancelled claim 27 in an effort to expedite prosecution of the present application.

In the Office Action, on page 2, final paragraph, the Examiner rejected claims 1-29 under 35 U.S.C. § 103(a) as being unpatentable over the teachings of Ting et al., United States Patent No. 6,372,254 in view of Mehta et al. United States Patent No. 5,837,284.

In response to this rejection, Applicants have canceled claims 2 and 23 and incorporated the subject matter of these claims into the pending independent claims, claims 1, 19 and 22. No new matter is added by these amendments. Applicants have also amended claim 19 to indicate that the immediate release component of the claimed composition is any type of immediate release dose and not just a layer. No new matter is added by this amendment. Support for this amendment can be found on page 2, lines 9-11 of the specification. Finally, Applicants have amended claims 1 and 25 to correct typographical errors.

All the currently pending claims are limited to a methylphenidate oral dosage forms that employ an immediate release portion and a controlled release portion. The controlled release portion further requires the presence of an enteric material to aid in controlling the release of the methylphenidate from the controlled release portion of the dosage form.

Applicants respectfully submit that the currently amended claims are patentable over the cited references either alone of combined because none of the cited references disclose or suggest to an individual of ordinary skill in the art an oral methylphenidate dosage formulation that employs an enteric material to aid in controlling the release of the methylphenidate.

The Ting reference teaches a press coated dosage form that contains an immediate release core surrounded by an extended release compartment which may be further coated with an optional instant release compartment. Col. 1, lines 7-22. The extended release compartment is prepared by compressing a blend of hydrophilic and hydrophobic polymers around the immediate release core. Col. 2, lines 50-57. The polymers used to prepare the extended release compartment are described in Col. 4, line 57 to Col. 5, line 15 of the Ting reference. This long list polymeric materials commonly used in the pharmaceutical industry includes only a few specific references to enteric materials, i.e shellac and zein, but provides no indication, suggestion of motivation that an enteric material should be used to control the release of methylphenidate. In fact, none of the working examples in the Ting reference employ an enteric material nor does the Ting reference list an enteric material among the preferred polymeric materials. See Col. 5,

lines 4-15. The Ting reference also fails to provide any specific working example of a dosage form that employs methylphenidate. The Ting reference only lists methylphenidate as a potential drug in a laundry list of over one hundred differnt drugs. Col. 3, line 39 to Col. 4, line 7.

It is respectfully submitted that the Ting reference fails to disclose or suggest the invention recited in the pending claims because the Ting reference fails to provide any disclosure or suggestion of a way to prepare an oral methylphenidate dosage form that employs an enteric material to control the release of the methylphenidate.

Although the Mehta reference discloses oral methylphenidate dosage forms that employ an immediate release dose and a controlled release dose, the Mehta reference fails to disclose or even remotely suggest the use of an enteric material to control the release of the methylphenidate. The Mehta reference only discloses the use of ammonio methacrylate copolymers to control the release of the methylphenidate. Col. 7, line 13-Col.8, line 57. Ammonio methacrylate copolymers are not enteric materials as evidenced by pp. 463 and 464 from the Handbook of Pharmaceutical Excipients, 4th ed. attached hereto as Exhibit A. Exhibit A is a section of the Handbook of Pharmaceutical Excipients 4th ed. that describes the various polymethacrylate copolymers that are commercially available and clearly indicates that the ammonio metharylate copolymers are not enteric materials .

It is respectfully submitted that the Mehta reference fails to disclose or suggest the invention recited in the pending claims because the Mehta reference fails to disclose or suggest a controlled release methylphenidate dosage formulation that employs an enteric

material to control the release of the methylphenidate.

The Ting and the Mehta references may disclose, among many other ingredients, the individual components recited in the amended claims, but neither reference discloses the unique combination of the methylphenidate and enteric material. Further, neither reference provides any motivation or suggestion to an individual of ordinary skill in the art to select an enteric material and use that material to control the release of methylphenidate as recited in the pending claims. Due to the unique chemical and physical properties of both methylphenidate and enteric materials, even if there was a suggestion to prepare a controlled release methylphenidate dosage form with an enteric material there is no guarantee that that it would results in a successful controlled release dosage form.

Based upon the foregoing amendments and representations, Applicants respectfully submit that the rejection of the claims in the above-identified application have been overcome and should be withdrawn. Early and favorable action is earnestly solicited.

Respectfully submitted,

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Handbook of Pharmaceutical Excipients

FOURTH EDITION

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Polymethacrylates

1 Nonproprietary Names

BP: Methacrylic acid–ethyl acrylate copolymer (1 : 1)
Methacrylic acid–ethyl acrylate copolymer (1 : 1) dispersion 30 per cent
Methacrylic acid–methyl methacrylate coploymer (1 : 1)
Methacrylic acid–methyl methacrylate copolymer (1 : 2)

PhEur: Acidum methacrylicum et ethylis acrylas polymerisatum 1 : 1
Acidum methacrylicum et ethylis acrylas polymerisatum 1 : 1 dispersio 30 per centum
Acidum methacrylicum et methylis methacrylas polymerisatum 1 : 1
Acidum methacrylicum et methylis methacrylas polymerisatum 1 : 2

USPNF: Ammonio methacrylate copolymer
Methacrylic acid copolymer
Methacrylic acid copolymer dispersion

Note that three separate monographs applicable to polymethacrylates are contained in the USPNF 20; *see* Section 9. Several different types of material are defined in the monographs. The PhEur 2002 contains four separate monographs applicable to polymethacrylates.

2 Synonyms

Eastacryl 30D; *Eudragit*; *Kollicoat MAE 30 D*; *Kollicoat MAE 30 DP*; polymeric methacrylates.

3 Chemical Name and CAS Registry Number

See Table I.

4 Empirical Formula and Molecular Weight

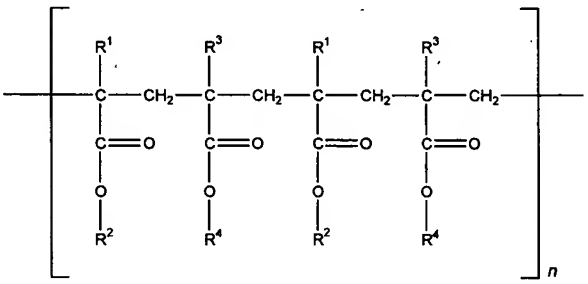
The PhEur 2002 describes methacrylic acid–ethyl acrylate copolymer (1 : 1) as a copolymer of methacrylic acid and ethyl acrylate having a mean relative molecular mass of about 250 000. The ratio of carboxylic groups to ester groups is about 1 : 1. It may contain suitable surfactants such as sodium dodecyl sulfate or polysorbate 80. An aqueous 30% w/v dispersion of this material is also defined in a separate monograph. Methacrylic acid–methyl methacrylate copolymer (1 : 1) is described in the PhEur 2002 as a copolymer of methacrylic acid and methyl methacrylate having a mean relative molecular mass of about 135 000. The ratio of carboxylic acid to ester groups is about 1 : 1. A further monograph in the PhEur 2002 describes methacrylic acid–methyl methacrylate copolymer (1 : 2), where the ratio of carboxylic acid to ester groups is about 1 : 2.

The USPNF 20 describes methacrylic acid copolymer as a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester. Three types, Type A, Type B, and Type C, are defined in the monograph. They vary in their methacrylic acid content and solution viscosity. Type C may contain suitable surface-active agents. Two additional polymers, Type A (*Eudragit RL*) and Type B (*Eudragit RS*), also referred to as ammonio methacrylate copolymers, consisting of fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups, are also described in the USPNF 20. A further monograph for an aqueous dispersion of Type C methacrylic acid copolymer is also defined.

See Section 9.

Typically, the molecular weight of the polymer is ⩾100 000.

5 Structural Formula



For *Eudragit E*:
R^1, R^3 = CH_3
R^2 = $CH_2CH_2N(CH_3)_2$
R^4 = CH_3, C_4H_9
For *Eudragit L* and *Eudragit S*:
R^1, R^3 = CH_3
R^2 = H
R^4 = CH_3
For *Eudragit RL* and *Eudragit RS*:
R^1 = H, CH_3
R^2 = CH_3, C_2H_5
R^3 = CH_3
R^4 = $CH_2CH_2N(CH_3)_3^+Cl^-$
For *Eudragit NE 30 D*:
R^1, R^3 = H, CH_3
R^2, R^4 = CH_3, C_2H_5
For *Eudragit L 30 D-55* and *Eudragit L 100-55*, *Eastacryl 30D*, *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*:
R^1, R^3 = H, CH_3
R^2 = H
R^4 = CH_3, C_2H_5

6 Functional Category

Film former; tablet binder; tablet diluent.

7 Applications in Pharmaceutical Formulation or Technology

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents.[1–15] Depending on the type of polymer used, films of different solubility characteristics can be produced; *see* Table II.

Table I: Chemical name and CAS Registry Number of polymethacrylates.

Chemical name	Trade name	Company name	CAS number
Poly(butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate) 1 : 2 : 1	*Eudragit E 100*	Röhm GmbH	[24938-16-7]
	Eudragit E 12.5	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate) 2 : 1	*Eudragit NE 30 D* (formerly *Eudragit 30 D*)	Röhm GmbH	[9010-88-2]
Poly(methacrylic acid, methyl methacrylate) 1 : 1	*Eudragit L 100*	Röhm GmbH	[25806-15-1]
	Eudragit L 12.5	Röhm GmbH	
	Eudragit L 12.5 P	Röhm GmbH	
Poly(methacrylic acid, ethyl acrylate) 1 : 1	*Eudragit L 30 D-55*	Röhm GmbH	[25212-88-8]
	Eudragit L 100-55	Röhm GmbH	
	Eastacryl 30D	Eastman Chemical	[25212-88-8]
	Kollicoat MAE 30 D	BASF Fine Chemicals	[25212-88-8]
	Kollicoat MAE 30 DP	BASF Fine Chemicals	
Poly(methacrylic acid, methyl methacrylate) 1 : 2	*Eudragit S 100*	Röhm GmbH	[25086-15-1]
	Eudragit S 12.5	Röhm GmbH	
	Eudragit S 12.5 P	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.2	*Eudragit RL 100*		[33434-24-1]
	Eudragit RL PO	Röhm GmbH	
	Eudragit RL 30 D	Röhm GmbH	
	Eudragit RL 12.5	Röhm GmbH	
Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1	*Eudragit RS 100*		[33434-24-1]
	Eudragit RS PO	Röhm GmbH	
	Eudragit RS 30 D	Röhm GmbH	
	Eudragit RS 12.5	Röhm GmbH	

Eudragit E is used as a plain or insulating film former; it is soluble in gastric fluid below pH 5. In contrast, *Eudragit L* and *S* types are used as enteric coating agents because they are resistant to gastric fluid. Different types are available that are soluble at different pH values: e.g., *Eudragit L 100* is soluble at pH > 6; *Eudragit S 100* is soluble at pH > 7.

Eudragit RL, *RS*, and *NE 30 D* are used to form water-insoluble film coats for sustained-release products. *Eudragit RL* films are more permeable than those of *Eudragit RS*, and films of varying permeability can be obtained by mixing the two types together.

Eudragit L 30 D-55 is used as an enteric coating film former for solid-dosage forms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5.

Eudragit L 100-55 is an alternative to *Eudragit L 30 D-55*. It is commercially available as a redispersible powder.

Eastacryl 30D, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP*, are aqueous dispersions of methacrylic acid–ethyl acrylate copolymers. They are also used as enteric coatings for solid-dosage forms.

Polymethacrylates are also used as binders in both aqueous and organic wet-granulation processes. Larger quantities (5–20%) of dry polymer are used to control the release of an active substance from a tablet matrix. Solid polymers may be used in direct-compression processes in quantities of 10–50%.

Polymethacrylate polymers may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration.[16]

See also Section 18.

8 Description

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Several different types are commercially available and may be obtained as the dry powder, as an aqueous dispersion, or as an organic solution. A (60 : 40) mixture of acetone and propan-2-ol is most commonly used as the organic solvent. *See* Tables I and III.

Eudragit E is cationic polymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters. It is soluble in gastric fluid as well as in weakly acidic buffer solutions (up to pH ≈ 5). *Eudragit E* is available as a 12.5% ready-to-use solution in propan-2-ol–acetone (60 : 40). It is light yellow in color with the characteristic odor of the solvents. Solvent-free granules contain ≈98% dried weight content of *Eudragit E*.

Eudragit L and *S*, also referred to as methacrylic acid copolymers in the USPNF 20 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1 : 1 in *Eudragit L* and approximately 1 : 2 in *Eudragit S*. Both polymers are readily soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alkalis, thus affording film coats that are resistant to gastric media but soluble in intestinal fluid. They are available as a 12.5% solution in propan-2-ol without plasticizer (*Eudragit L 12.5* and *S 12.5*); and as a 12.5% ready-to-use solution in propan-2-ol with 1.25% dibutyl phthalate as plasticizer (*Eudragit L 12.5 P* and *S 12.5 P*). Solutions are colorless, with the characteristic odor of the solvent. *Eudragit L-100* and *Eudragit S-100* are white free-flowing powders with at least 95% of dry polymers.

Table II: Summary of properties and uses of commercially available polymethacrylates.

Type	Supply form	Polymer dry weight content	Recommended solvents or diluents	Solubility	Applications
Eudragit (Röhm GmbH)					
Eudragit E 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit E 100	Granules	98%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit L 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L 100-55	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit L 30 D-55	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Eudragit S 12.5 P	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit S 100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit RL 12.5	Organic solution	12.5%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL 100	Granules	97%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL PO	Powder	97%	Acetone, alcohols	High permeability	Sustained release
Eudragit RL 30 D	Aqueous dispersion	30%	Water	High permeability	Sustained release
Eudragit RS 12.5	Organic solution	12.5%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 100	Granules	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS PO	Powder	97%	Acetone, alcohols	Low permeability	Sustained release
Eudragit RS 30 D	Aqueous dispersion	30%	Water	Low permeability	Sustained release
Eudragit NE 30 D	Aqueous dispersion	30% or 40%	Water	Swellable, permeable	Sustained release, tablet matrix
Eastacryl (Eastman Chemical Company)					
Eastacryl 30 D	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Kollicoat (BASF Fine Chemicals)					
Kollicoat 30 D	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings
Kollicoat 30 DP	Aqueous dispersion	30%	Water	Soluble in intestinal fluid from pH 5.5	Enteric coatings

Note: Recommended plasticizers for the above polymers include dibutyl phthalate, polyethylene glycols, triethyl citrate, triacetin, and 1,2-propylene glycol. The recommended concentration of the plasticizer is approximately 10–25% plasticizer (based on the dry polymer weight). A plasticizer is not necessary with *Eudragit E 12.5*, *Eudragit E 100* and *Eudragit NE 30 D*.

Eudragit RL and *Eudragit RS*, also referred to as ammonio methacrylate copolymers in the USPNF 20 monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters, with *Eudragit RL* (Type A) having 10% of functional quaternary ammonium groups and *Eudragit RS* (Type B) having 5% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to pH-independent permeability of the polymers. Both polymers are water-insoluble, and films prepared from *Eudragit RL* are freely permeable to water, whereas, films prepared from *Eudragit RS* are only slightly permeable to water. They are available as 12.5% ready-to-use solutions in propan-2-ol–acetone (60 : 40). Solutions are colorless or slightly yellow in color, and may be clear or slightly turbid; they have an odor characteristic of the solvents. Solvent-free granules (*Eudragit RL 100* and *Eudragit RS 100*) contain ⩾97% of the dried weight content of the polymer.

Eudragit RL PO and *Eudragit RS PO* are fine, white powders with a slight aminelike odor. They are characteristically the same polymers as *Eudragit RL* and *RS*. They contain ⩾97% of dry polymer.

Eudragit RL 30 D and *Eudragit RS 30 D* are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. The dispersions contain 30% polymer. The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers. Films prepared from *Eudragit RL 30 D* are readily permeable to water and to dissolved active substances, whereas films prepared from *Eudragit RS 30 D* are less permeable to water. Film coatings prepared from both polymers give pH-independent release of active substance. Plasticizers are usually added to improve film properties.

Table III: Solubility of commercially available polymethacrylates in various solvents.

Type	Solvent						
	Acetone and alcohols[a]	Dichloromethane	Ethyl acetate	1 N HCl	1 N NaOH	Petroleum ether	Water
Eudragit (Röhm GmbH)							
Eudragit E 12.5	M	M	M	M	–	M	–
Eudragit E 100	S	S	S	–	–	I	I
Eudragit L 12.5 P	M	M	M	–	M	P	P
Eudragit L 12.5	M	M	M	–	M	P	P
Eudragit L 100-55	S	I	I	–	S	I	I
Eudragit L 100	S	I	I	–	S	I	I
Eudragit L 30 D-55[b]	M[c]	–	–	M[d]	–	M	
Eudragit S 12.5 P	M	M	M	–	M	P	P
Eudragit S 12.5	M	M	M	–	M	P	P
Eudragit S 100	S	I	I	–	S	I	I
Eudragit RL 12.5	M	M	M	–	–	P	M
Eudragit RL 100	S	S	S	–	–	I	I
Eudragit RL PO	S	S	S	–	I	I	I
Eudragit RL 30 D	M[e]	M	M	–	I	I	M
Eudragit RS 12.5	M	M	M	–	–	P	M
Eudragit RS 100	S	S	S	–	–	I	I
Eudragit RS PO	S	S	S	–	I	I	I
Eudragit RS 30 D	M[e]	M	M	–	I	I	M
Eastacryl (Eastman Chemical Company)							
Eastacryl 30D[b]	M[c]	–	–	–	M[d]	–	M
Kollicoat (BASF Fine Chemicals)							
Kollicoat MAE 30 D[b]	M[c]	–	–	–	M[d]	–	M
Kollicoat MAE 30 DP[b]	M[c]	–	–	–	M[d]	–	M

S = soluble; M = miscible; I = insoluble or immiscible; P = precipitates.

[a] Alcohols including ethanol, methanol, and propan-2-ol.

[b] Supplied as a milky-white aqueous dispersion.

[c] A 1 : 5 mixture forms a clear, viscous, solution.

[d] A 1 : 2 mixture forms a clear or slightly opalescent, viscous liquid.

1 part of *Eudragit RL 30 D* or of *Eudragit RS 30 D* dissolves completely in 5 parts acetone, ethanol, or propan-2-ol to form a clear or slightly turbid solution. However, when mixed in a ratio of 1 : 5 with methanol, *Eudragit RL 30 D* dissolves completely, whereas *Eudragit RS 30 D* dissolves only partially.

Eudragit NE 30 D is an aqueous dispersion of a neutral copolymer consisting of polymethacrylic acid esters. The dispersions are milky-white liquids of low viscosity and have a weak aromatic odor. Films prepared from the lacquer swell in water, to which they become permeable. Thus, films produced are insoluble in water, but give pH-independent drug release.

Eudragit L 30 D-55, is an aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer corresponds to USPNF 20 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1 : 1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media but soluble in the small intestine.

Eastacryl 30D, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP* are also aqueous dispersions of the anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer also corresponds to USPNF 20 methacrylic acid copolymer, Type C. The ratio of free-carboxyl groups to ester groups is 1 : 1. Films prepared from the copolymers dissolve above pH 5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media, but soluble in the small intestine.

Eudragit L 100-55 (prepared by spray-drying *Eudragit L 30 D-55*) is a white, free-flowing powder that is redispersible in water to form a latex that has properties similar to those of *Eudragit L 30 D-55*.

9 Pharmacopeial Specifications

Specifications for polymethacrylates from the PhEur 2002 are shown in Table IV and those from the USPNF 20 in Table V.

10 Typical Properties

Acid value:
- 300–330 for *Eudragit L 12.5*, *L 12.5 P*, *L 100*, *L 30 D-55*, *L 100-55*; *Eastacryl 30D*; *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP*
- 180–200 for *Eudragit S 12.5*, *S 12.5 P*, and *S 100*

Alkali value:
- 162–198 for *Eudragit E 12.5* and *E 100*
- 23.9–32.3 for *Eudragit RL 12.5*, *RL 100*, and *RL PO*
- 27.5–31.7 for *Eudragit RL 30 D*
- 12.1–18.3 for *Eudragit RS 12.5*, *RS 100*, and *RS PO*
- 16.5–22.3 for *Eudragit RS 30 D*

Density (bulk): 0.390 g/cm^3

Density (tapped): 0.424 g/cm^3

Table IV: Specifications from PhEur 2002.

Test	PhEur 2002			
	Methacrylic acid–ethyl acrylate copolymer (1 : 1)	Methacrylic acid–ethyl acrylate copolymer (1 : 1) dispersion 30%	Methacrylic acid–methyl methacrylate copolymer (1 : 1)	Methacrylic acid–methyl methacrylate copolymer (1 : 2)
Identification	+	+	+	+
Characters	+	+	+	+
Appearance of a film	+	+	+	+
Apparent viscosity	+	⩽15 mPa s	50–200 mPa s	–
Particulate matter	–	⩽1.0%	–	–
Ethyl acrylate and methacrylic acid	⩽0.1%	⩽0.1%	–	–
Methyl methacrylate and methacrylic acid	–	–	⩽0.1%	⩽0.1%
Residue on evaporation	–	28.5–31.5%	–	–
Loss on drying	⩽5.0%	–	⩽5.0%	⩽5.0%
Sulfated ash	⩽0.4%	⩽0.2%	⩽0.1%	⩽0.1%
Microbial contamination	–	+	–	–
Assay (methacrylic acid units)	46.0–50.6%	46.0–50.6%	46.0–50.6%	27.6–30.7%

Density (true):
- 0.811–0.821 g/cm^3 for *Eudragit E*
- 0.83–0.85 g/cm^3 for *Eudragit L, S 12.5* and *12.5 P*
- 0.831–0.852 g/cm^3 for *Eudragit L, S 100*
- 1.062–1.072 g/cm^3 for *Eudragit L 30 D-55*
- 0.821–0.841 g/cm^3 for *Eudragit L 100-55*
- 0.816–0.836 g/cm^3 for *Eudragit RL* and *RS 12.5*
- 0.816–0.836 g/cm^3 for *Eudragit RL* and *RS PO*
- 1.047–1.057 g/cm^3 for *Eudragit RL* and *RS 30 D*
- 1.037–1.047 g/cm^3 for *Eudragit NE 30D*
- 1.062–1.072 g/cm^3 for *Eastacryl 30D*
- 1.062–1.072 g/cm^3 for *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*

Refractive index:
- n_D^{20} = 1.38–1.385 for *Eudragit E*
- n_D^{20} = 1.39–1.395 for *Eudragit L* and *S*
- n_D^{20} = 1.387–1.392 for *Eudragit L 100-55*
- n_D^{20} = 1.38–1.385 for *Eudragit RL* and *RS*

Solubility: *see* Table II.

Viscosity (dynamic):
- 3–12 mPa s for *Eudragit E*
- ⩽50 mPa s for *Eudragit NE 30D*
- 50–200 mPa s for *Eudragit L* and *S*
- ⩽15 mPa s for *Eudragit L 30 D-55*
- 100–200 mPa s for *Eudragit L 100-55*
- ⩽15 mPa s for *Eudragit RL* and *RS*
- ⩽200 mPa s for *Eudragit RL* and *RS 30D*
- ⩽15 mPa s for *Kollicoat MAE 30 D* and *Kollicoat MAE 30 DP*
- 145 mPa s for *Eastacryl 30D*

11 Stability and Storage Conditions

Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can readily be broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

Dispersions are sensitive to extreme temperatures and phase separation occurs below 0°C. Dispersions should therefore be stored at temperatures between 5 and 25°C and are stable for at least 18 months after shipping from the manufacturer's warehouse if stored in a tightly closed container at the above conditions.

12 Incompatibilities

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; *see* Table II. For example, dispersions of *Eudragit L 30 D*, *RL 30 D*, *L 100-55*, and *RS 30 D* are incompatible with magnesium stearate. *Eastacryl 30D*, *Kollicoat MAE 30 D*, and *Kollicoat MAE 30 DP* are also incompatible with magnesium stearate.

Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

13 Method of Manufacture

Prepared by the polymerization of acrylic and methacrylic acids or their esters, e.g., butyl ester or dimethylaminoethyl ester.

14 Safety

Polymethacrylate copolymers are widely used as film-coating materials in oral pharmaceutical formulations. They are also used in topical formulations and are generally regarded as nontoxic and nonirritant materials.

A daily intake of 2 mg/kg body-weight of *Eudragit* (equivalent to approximately 150 mg for an average adult) may be regarded as essentially safe in humans.

See also Section 15.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Additional measures should be taken when handling organic solutions of polymethacrylates. Eye protection, gloves, and a dust mask or respirator are recommended. Polymethacrylates should be handled in well-ventilated environment and measures should be taken to prevent dust formation.

Table V: Specifications from USPNF 20.

Test	USPNF 20	USPNF 20 (Suppl 1)
	Ammonio methacrylate copolymer[a]	Methacrylic acid copolymer
Identification	+	+
Viscosity		
Type A	≤15 mPa s	50–200 mPa s
Type B	≤15 mPa s	50–200 mPa s
Type C	–	100–200 mPa s
Loss on drying		
Type A	≤3.0%	≤5.0%
Type B	≤3.0%	≤5.0%
Type C	–	≤5.0%
Residue on ignition		
Type A	≤0.1%	≤0.1%
Type B	≤0.1%	≤0.1%
Type C	–	≤0.4%
Arsenic	–	≤2 ppm
Heavy metals	≤0.002%	≤0.002%
Organic volatile impurities	–	+
Limit of monomers	–	≤0.05%
Methyl methacrylate	≤0.005%	–
Ethyl acrylate	≤0.025%	–
Assay of methacrylic acid units (dried basis)		
Type A	8.85–11.96%	46.0–50.6%
Type B	4.48–6.77%	27.6–30.7%
Type C	–	46.0–50.6%

[a] Corresponds to *Eudragit RL* and *RS*.

Acute and chronic adverse effects have been observed in workers handling the related substances methyl methacrylate and poly(methyl methacrylate) (PMMA).[17,18] In the UK, the occupational exposure limit for methyl methacrylate has been set at 208 mg/m^3 (50 ppm) long-term (8-hour TWA), and 416 mg/m^3 (100 ppm) short-term.[19]

See also Section 17.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (oral capsules and tablets). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Methyl methacrylate; poly(methyl methacrylate).

Methyl methacrylate

Empirical formula: $C_5H_8O_2$
Molecular weight: 100.13
CAS number: [80-62-6]
Synonyms: methacrylic acid, methyl ester; methyl 2-methacrylate; methyl 2-methylpropenoate; MME.
Safety:

LD_{50} (dog, SC): 4.5 g/kg
LD_{50} (mouse, IP): 1 g/kg
LD_{50} (mouse, oral): 5.2 g/kg
LD_{50} (mouse, SC): 6.3 g/kg
LD_{50} (rat, IP): 1.33 g/kg
LD_{50} (rat, SC): 7.5 g/kg

Comments: methyl methacrylate forms the basis of acrylic bone cements used in orthopedic surgery.

Poly(methyl methacrylate)

Empirical formula: $(C_5H_8O_2)_n$
Synonyms: methyl methacrylate polymer; PMMA.
Comments: poly(methyl methacrylate) has been used as a material for intraocular lenses, for denture bases, and as a cement for dental prostheses.

18 Comments

A number of different polymethacrylates are commercially available that have different applications and properties; *see* Table II.

For spray coating, polymer solutions and dispersions should be diluted with suitable solvents. Some products need the addition of a plasticizer such as dibutyl sebacate, dibutyl phthalate, glyceryl triacetate, or polyethylene glycol. Different types of plasticizer may be mixed to optimize the polymer properties for special requirements.

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